REMARKS/ARGUMENTS

By this Amendment, claims 7, 18, 21, and 27 are amended. Claims 1-5, 7, 10-16, 18, 21-25, 27, 30-61 are pending.

Citations to the Specification are directed to U.S. Patent Application No. 2007/0100143 (Reddy).

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Rejection under 35 USC 112 second paragraph

Claim 16, 34-46 and 51-61 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is respectfully traversed.

The Examiner argues that claim 16 recites the term "anti-solvent" which has indefinite metes and bounds because there is no definition for said term in the specification. It is unclear if this is another reagent, or a device, or a process. The Examiner argues that However, the specification does not describe what is considered an "anti-solvent". Thus, it is not clear from the claims or the specification what is used as an "anti-solvent" to cool, seed or partially remove solvent.

The Examiner argues that claim 16 recites the term "anti-solvent," which has indefinite metes and bounds because there is no definition for said term in the specification, and alleges that it is unclear if this is another reagent, or a device, or a process.

In reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph "by providing clear warning to others as to what constitutes infringement of the patent". See, e.g., Solomon v. Kimberly-Clark Corp., 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000). MPEP 2173.02, MPEP 2173.02.

In the instant case, the Specification provides a definition for the term "anti-solvent," and one of skill in the art is apprised of its scope. For example, U.S. Patent No. 4,668,768 (Mendiratta et al.) describes an anti-solvent as follows ('768 col. 2, lines):

> The term "organic anti-solvent" for a polymer refers to those solvents which, when added in a sufficient quantity, cause a polymer to precipitate from a solution without removal or reduction of the solvent medium. This is to be distinguished from non-solvents, which do not effect the solubility of a polymer within a solution when introduced in any quantity. The polymer is insoluble in both non-solvents and anti-solvents, but to precipitate a polymer by addition of a non-solvent, the solvent for the polymer must be removed.

Thus, give the definition in the Specification at (¶[0011]), and (¶[0015], that the anti-solvent is added to initiate or force crystallization of a solute from a solution. Accordingly, one skilled in the art would understand what is claimed when the claim is read in light of the specification.

The Examiner argues that claim 34 and claims dependent thereon recite the limitation of "activated tetrahydro-2-furoic acid" which is not clear how it differs from the usual tetrahydro-2-furoic acid. Applicant has previously cited the Specification at (¶[0020]) as teaching that "Activated tetrahydro-2-furoic acid refers to tetrahydro-2-furoic acid having its carboxylic acid group in a conventional activated form," however, the Examiner argues that such an explanation does not clearly define the activated form.

However, the Specification provides a definition for the term "activated tetrahydro-2-furoic acid," and one of skill in the art is apprised of its scope. For example, WO2004/022629 (Kozlowski et al.) discloses carboxylic acid groups in activated form:

> Sometimes, however, it is necessary to form an"activated"version of the carboxylic acid in order to enhance reactivity to the biologically active agent or surface. Methods for activating carboxylic acids are known in the art and include, for example, dissolving the water-soluble polymer bearing a terminal carboxylic acid in methylene chloride and subsequently adding N-hydroxysuccinimide and N, N-dicyclohexylcarbodiimide (DCC) to form an activated N-succinimidyl ester version of the carboxylic acid. Other approaches for activating a carboxylic acid are known to those of ordinary skill in the art.

Thus, give the definition in the Specification at (¶[0020]), that activated tetrahydro-2-furoic acid refers to tetrahydro-2-furoic acid having its carboxylic acid group in a conventional activated form. Accordingly, one skilled in the art would understand what is claimed when the

claim is read in light of the specification. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

The Examiner has rejected claims 7, 18 and 27 as being dependent on cancelled claims. The claims have been amended herein. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 USC 102

Claim 1-8, 12-19, 21, 23, 34-36, 39, 41, 43, and 45-50 stand rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 4,315,007 (Manoury). This rejection is respectfully traversed.

The Examiner argues that '007 describes the process of making the free base of alfuzosin by reacting N_1-Methyl-N2-tetrahydrofuroylpropylenediamine (otherwise known as "the above amine") with 4-amino-2-chloro-6,7-dimethoxyquinazoline in isoamyl alcohol and then heated which produces a "precipitate" that is the free base of alfuzosin which at this point gets "crystallized from a mixture of ethanol and ether". The Examiner argues that the HCl salt at the end requires an additional step of acid addition salt which is not described because there is no mention of adding HCl acid prior to the step of crystallization the free base in ethanol and ether. The Examiner argues that in particular, Example I teaches the crystalline form of alfuzosin base, and Example II teaches the acid addition salt of said base. Thus, it is clear that both Examples I and II yield the free base of alfuzosin.

In Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) (MPEP 2131), the CAFC set forth that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference". In the instant case, not every element of the claims is present in the '007 patent.

Here, the claims are directed to crystalline alfuzosin base, and contrary to the Examiners' argument, the Examples do not teach the isolation of crystalline alfuzosin base. Example 1, cited by the Examiner, refers to the crystallization of the hydrochloride salt, not the base ('007, column 3, lines 21-25):

> This yields a precipitate which is combined with the first and the whole is cyrstallised from a mixture of ethanol and ether. N_1-(4-Amino-6,7-dimethoxyquinazol-2-yl)-N_1-methyl-N_2-(tetrahydrofuroyl-2)-propylenediamine hydrochloride, which melts at 235°C (decomposition), is thus obtained.

The Examiner admits that (Office Action at page 5):

> ...the HC1 salt at the end requires an additional step of acid addition salt which is not described because there is no mention of adding HCl acid prior to the step of crystallization the free base in ethanol and ether.

There is no teaching in Example I of producing the free base of alfuzosin. In addition, Example II of the '007 patent referring to crystallization is directed to crystallization of alfuzosin hydrochloride ('007, column 4, lines 3-11), and does not teach producing the free base.

If the Examiner is arguing that the '007 patent inherently discloses alfuzosin free base, then the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Here, the Examiner has not met that burden by arguing that Applicant needs to show the absence of an alleged effect. "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

If the Examiner is aware of, or alleges to have some knowledge that the '007 patent produces alfuzosin free base, then the Examiner should provide such knowledge. It would not be appropriate for the examiner to take official notice of facts without citing a prior art reference where the facts asserted to be well known are not capable of instant and unquestionable demonstration as being well-known. For example, assertions of technical facts in the areas of esoteric technology or specific knowledge of the prior art must always be supported by citation

to some reference work recognized as standard in the pertinent art. In re Ahlert, 424 F.2d at 1091, 165 USPQ at 420-21. If applicant adequately traverses the examiner's assertion of official notice, the examiner must provide documentary evidence in the next Office action if the rejection is to be maintained. See 37 CFR 1.104(c)(2). See also Zurko, 258 F.3d at 1386, 59 USPQ2d at 1697 ("[T]he Board [or examiner] must point to some concrete evidence in the record in support of these findings" to satisfy the substantial evidence test). If the examiner is relying on personal knowledge to support the finding of what is known in the art, the examiner must provide an affidavit or declaration setting forth specific factual statements and explanation to support the finding. See 37 CFR 1.104(d)(2).

The instant claims are directed to a crystalline form of alfuzosin base and processes for the preparation of crystalline alfuzosin base, which are not disclosed in the '007. In addition, the '007 patent clearly does not teach crystalline alfuzosin base of a purity of 95% or 99%. Since the instant claims are directed to a crystalline form of alfuzosin base and processes for the preparation of crystalline alfuzosin base, which are not disclosed in the '007, the claims are not anticipated.

Accordingly, reconsideration and withdrawal of the rejection of the claims is respectfully requested.

Rejection under 35 USC 103

Claims 9-11, 20, 22, 24-33, 37, 38, 40, 42, 44 and 51-61 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 4,315,007 (Manoury). This rejection is respectfully traversed.

The Examiner argues that said claims recite a process of crystallizing alfuzosin by using specific solvents such as: methyl-isobutyl ketone, methanol, ethanol which are not disclosed in Example I or II of Manoury. However, methyl-isobutyl ketone and acetone are both ketones having dipole moments that are close enough to allow one skilled in the art to replace methyl-isobutyl ketone with acetone for cost effective (see a print out from Wikipedia, keyword "Acetone"). Likewise, isoamyl alcohol and ethanol are both alcohols and have similar polarity, and would be exchangeable (see Wikipedia, keyword "Alcohol").

The Examiner further argues that Example I of the '007 patent teaches the crystalline alfuzosin base as the final product crystallized from a mixture of ethanol and ether. Example II teaches the step of acid addition salt of the alfuzosin base (otherwise known as the "residual amine") by adding ethanolic hydrogen chloride to the alfuzosin base in 2-propanol.The Examiner argues that Manoury's teaching uses solvents that have similar polarity and pH, and so, it would have been reasonable to expect a crystalline form from alfuzosin base.

However, the claims are patentable over the '007 patent for the following reasons. The framework for the objective analysis for determining obviousness under 35 U.S.C. § 103 is stated in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966). Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows: (A) Determining the scope and content of the prior art; and (B) Ascertaining the differences between the claimed invention and the prior art; and (C) Resolving the level of ordinary skill in the pertinent art. To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385 (CCPA 1970). MPEP 2143.03. It is important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. (KSR v Teleflex, 12 S.Ct. 1727, 1740 (US 2007)).

Here, the claims are drawn to crystalline alfuzosin base, and a process for the preparation of crystalline alfuzosin base which comprises stirring a suspension of impure or noncrystalline alfuzosin base in a ketonic solvent selected from the group consisting of methyl ethyl ketone, methyl isobutyl ketone, methyl isopropyl ketone, methyl tert-butyl ketone, and mixtures thereof or an alcoholic solvent selected from the group consisting of methanol, ethanol, tert-butyl alcohol and mixtures thereof.

However, there is not a reasonable expectation that different solvents would result in the formation of crystalline alfuzosin base because it is known in the art that the use of different solvents will produce different crystalline forms of a product, as taught in the Banga et al. reference. The Examiner refers to solvent polarity, but cotes no reference to establish the polarities of the solvents, and no reference to stand show that these would

produce the same form. As the Banga reference, the assumption that crystallization from different solvents will yield the crystalline alfuzosin base, has no basis in fact.

Accordingly, reconsideration and withdrawal of the rejection of the claims is respectfully requested.

* * *

For at least the reasons set forth above, it is respectfully submitted that the above-identified application is in condition for allowance. Favorable reconsideration and prompt allowance of the claims are respectfully requested.

Should the Examiner believe that anything further is desirable in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.

May 5, 2011

By_____

Joseph F. Murphy
Registration No. 58,313
Customer No. 03000
(215) 567-2010
Attorneys for Applicants

Please charge or credit our Account No. 03-0075 as necessary to effect entry and/or ensure consideration of this submission.